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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/792,374	LEVY ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-76* is/are pending in the application.

4a) Of the above claim(s) *13-39 and 57-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 40-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/10/04 and 10/4/04 and 5/5/05*. 2127/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Office decides to reopen the prosecution in view of the reconsideration and new ground of rejection ser forth below. The office apologizes for the delay of the prosecution for this case. Thus, this office action is written in response to the papers received 8/15/05. Applicant's election with traverse of Group I (claims 1-12 and 40-56) is acknowledged.

The traversal is on the ground(s) that significant overlap in the claimed subject matter, searching classes, and examination, especially in Groups II and III, poses no undue burden to the examiner.

These have been considered, but not found persuasive. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). The group II and III are two distinct inventions, which are drawn to the methods having different method steps and different effects. The methods require different patient populations. Search of two methods are not co-extensive in non-patent literature and US patent database, which would impose a serious search burden. For this reason, the restriction requirement is deemed to be proper and is adhered to. The requirement is therefore made **FINAL**.

Claims 1-76 are pending. Claims 13-39 and 57-76 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Claims 1-12 and 40-56 will be examined on the merits.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 9/10/04, 10/4/04, 5/5/05, AND 2/27/06 are considered by the examiner and initialed copy of the PTO-1449 is enclosed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 40-56 are vague and indefinite in the recitations of " a kit comprising assays for measuring expression of gene" in claim 40. Although the claims are drawn to a product, the claims do not contain any tangible component in the claims. It is not clear what will be used in the kit for measuring expression of a plurality of gene in a tumor sample. This rejection can be obviated by amending the claims by adding the product, such as primers with specific SEQ ID Nos. Claim 40 renders claim 41-50 indefinite.

2. Claims 40-56 are vague and indefinite in the recitation of "**stratifies** " in claim 40. It is not clear the exact meaning of "**stratifies** ". Therefore, the metes and bounds of the claims cannot be determined. Furthermore, claim 40 also renders the dependent claims indefinite.

3. Claims 6, 7 and 49-53 are vague and indefinite in the recitation of "gene, PGK1, GAPDH, LMO2, CCND2, SCYA3 ..... " as the sole means. The use of laboratory designations to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. This rejection can be obviated by amending the claims to specifically and uniquely identify each expressed gene product, for example, by SEQ ID NO.

4. Claims 53-56 are vague and indefinite in the recitations of "about" for the factor A, B, C, D, E and F in the claims. The specification on page 25 teaches a formula for predicting survival rate of a patient with DLBCL gene expression with defined numbers for A, B, C, D, E and F (page 25, para 43). The specification does not provide any information indicating the ranges of "about" or the number can be altered in the formula. Therefore, the metes and bounds of the claims cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

As drawn to written description—Plurality of genes

Claims 1-12, 40-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims encompass a method of for classifying a patient having diffuse large B-cell lymphoma (DLBCL) comprising provide a plurality of primer to hybridize to a plurality of primers. The claims also drawn to a kit comprising assays fro measuring expression of the plurality of genes in tumor samples.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

The specification on table 2 (page 14-20) lists 36 genes with accession No and primers or probes for detecting the gene expression. The specification on table 3 teaches the expression of these genes in patient samples and Raji cells. However, when further classifying or predicting the survival of the patients with DLBCL, the specification only analyze the expressing six of the gene products, LMO, BCL6, FN1, CCND2, SCYA3, and BCL-2 in a survival prediction model. The specification neither discloses other gene products, which are associated with the survival rate of the patients, nor disclose how to classify the DLBCL patients with the expressions of the other genes.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. In the instant application, the method or kit are claiming to classify a patient having DLBCL by assaying a plurality of gene expressions based on a working example of analyzing limited number of gene expressions. Without

assay more gene expression in more patients with DLBCL, one of skill in the art would reasonably conclude that the disclosure fails to provide a method of classifying a patient with DLBCL by measuring, normalizing and correlating a plurality of gene expressions.

Therefore, only the method for predicting a survival of a patients having DLBCL by measuring, normalizing and correlating the expression of LMO, BCL6, FN1, CCND2, SCYA3, and BCL-2, and kit containing the components for detecting the above gene expression not others meet the written description requirement. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicant has been reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 1115).

Applicant has been directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001. Also, see MPEP 2163.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claims 1-3, 8-9, and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Alizadeh et al., (Nature, Vol 403, page 503-511, February 2000).

Claim 1 is drawn to a method for classifying a patient having diffuse large B-cell lymphoma (DLBCL), comprising measuring expression of a plurality of genes, in a tumor sample form the patient and correlating normalized tumor expression values to normalized reference expression values obtained for the plurality of genes from DLBCL patients in the classification groups. Claims 2-3 are further drawn to claim 1, wherein the genes are predictive of survival after anthracycline-based thermotherapy. Claims 8-10 are further drawn to claim 1, wherein normalize tumor expression values and normalized reference expression values comprises ratios of expression values in DLBCL to expression in a reference cell line, Raji. Claim 12 is further drawn to claim 2, wherein the gene expression is similar to normalized reference expression values after anthracycline-based chemotherapy.

Alizadeh et al., disclose a method of classifying a patient having a DLBCL, comprising measuring expression of a plurality of genes in tumor samples from patient having DLBCL and correlating the gene expressions in the classification groups. Alizadeh et al., disclose the levels of expressing LMO2, BCL-6, BCL-2 from the samples of DLBCL patients normalized to the control expression comprising Raji cell (page 508-509 and fig 4, and page 510, column 2, para 2). Alizadeh et al., also disclose that method predicts the correlation of patient survival with gene expression in the classification groups comprises overall survival after treatment with anthracycline-based chemotherapy (page 509, column 2, fig 5 and page 510, line 15-19).

2. Claims 1-3, 8, and 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Rosenwald et al., (N Engl J Med, vol 346, page 1937-47, June, 2002) or Rocke et al., (US Patent Publication, 2002/0111742, Aug, 15, 2002)

Claims 1-3, 8, and 12 are set forth above. Claims 10-11 are further drawn to claims 1 and 2, wherein the expression value of plurality of gene from DLBCL patients have been stratified based on the performance of univariate Cox proportional hazards analysis with the classification.

Rosenwald et al., disclose a method of classifying a patient having a DLBCL, comprising measuring expression of a plurality of genes in tumor samples from patient having DLBCL and correlating the gene expression in the classification groups (table 1, 2, and .fig 3). Rosenwald et al., disclose that the

levels of plurality of genes from the samples of DLBCL patients and prediction of patient survival in the classification are determined using the Cox proportional hazards model and univariate analysis of the groups (page 1938, column 2, para 1 and page 1944, column 1, para 2). Rosenwald et al., disclose that the method is used to formulate a molecular predictor of survival after anthracycline-based chemotherapy for DLBCL (abstract, page 1937).

Rocke et al., disclose a method of classifying a patient having a DLBCL, comprising measuring expression of a plurality of genes in tumor samples from patient having DLBCL and correlating the gene expression in the classification group (page 1, para 6). Rocke et al., also disclose that prediction of patient survival in the classification is determined using the Cox proportional hazards model and univariate analysis of the groups (page 13, para 112).

3. Claims 1-2, 4-6, 8, 10-11, 40-41, 43-45 and 49 are rejected under 35 U.S.C. 102(e) as being anticipated by Gordon et al., (US Patent application Publication, 20030219760, effective filing date, Aug 30, 2002).

Claims 1-2, 4-6, 8, 10-11 are set forth above.

Claims 40 is drawn to a kit comprising assays for measuring expression of a plurality of genes of a tumor from a patient having DLBCL, wherein the expression of the plurality of genes is normalized and stratifies the patients into classification groups. Claim 41 is further drawn to claim 40, wherein gene expression is classified in groups predictive of survival. Claims 43-45 are further drawn to claim 40, wherein the assays is RT-PCR assay, which normalized to housekeeping gene. Claim 49 is further drawn to claim 40, wherein the genes comprise FN.

Gordon et al., disclose a kit for a cancer diagnosis comprising measuring the expression of a plurality of genes and analysis of ratio of the expression in cancer cells or cancer samples from patients (page 2, para 20). Gordon et al., disclose RT-PCR method for measuring the gene expression of the tumor samples or further confirming the microarray result for the gene expressions, comprising the expression of fibronectin (FN), using internal control, GAPDH, as a housekeeping gene (page 4 and fig and page 19, para 182). Gordon et al., also disclose diagnosing and predicting the survival of DLBCL

patients using the expression profile of plurality of genes (figure 5-9, page 29, para 247, and page 39-40, table 17-20).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 1 and 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenwald et al., (N Engl J Med, vol 346, page 1937-47, June, 2002) in view of Gordon et al., (US Patent application Publication, 20030219760, effective filing date, Aug 30, 2002) and Goldberg et al., (US Patent Publication, 20030060439, effective filing date, 1/11/2001)

The teaching of Rosenwald et al., are set forth above in 102(b) rejection.

Rosenwald et al., do not teach the method of measuring expression by real time RT-PCR on the tumor samples and internal control of expressing PGK1.

Gordon et al., teach a method of real time quantitative RT-PCR (para 184 and 283). Gordon et al., also teach internal control of GAPDH as a housekeeping gene for the PCR (para 182). Gordon et al., teach RT-PCR method for measuring the gene expression of the tumor samples or further confirming the microarray result for the gene expressions, comprising the expression of fibronectin (FN), using internal control, GAPDH, as a housekeeping gene (page 4 and fig and page 19, para 182). Gordon et al., teach a

kit for a cancer diagnosis comprising measuring the expression of a plurality of genes and analysis of ratio of the expression in cancer cells or cancer samples from patients (page 2, para 20). Gordon et al., also teach diagnosing and predicting the survival of DLBCL patients using the expression profile of plurality of genes (figure 5-9, page 29, para 247, and page 39-40, table 17-20).

Goldberg et al., teach expression of mRNA, PGK1, as internal control of a housekeeping gene (para 46).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method for classifying a patient having a DLBCL, comprising measuring the expression of a plurality of genes in DLBCL tumors samples of Rosenwald et al.' teaching, and measuring the gene expression by real time RT-PCR of Gordon et al.'s teaching and normalizing the expression by PGK1 of Goldberg et al.'s teachings. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to combine the teachings of Rosenwald et al., Gordon et al., and Goldberg et al., to classify a patient having a DLBCL and predict the patient survival by the expression of gene determined by real time RT-PCR on DLBCL tumor samples because Rosenwald et al., have show a method of classifying DLBCL patients by expression of plurality of genes, Gordon et al., have shown measuring gene expression using real time RT-PCR normalized to a housekeeping gene. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use PGK1 as the housekeeping gene because as shown by Goldberg et al., PGK1 is a known housekeeping gene as an internal control of cellular mRNA.

2. Claims 40-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gordon et al., (US Patent application Publication, 20030219760, effective filing date, Aug 30, 2002) in view of by Alizadeh et al., (Nature, Vol 403, page 503-511, February 2000) and Goldberg et al., (US Patent Publication, 20030060439, effective filing date, 1/11/2001).

The teaching of Gordon et al., are described above in 102 (b) rejection.

Gordon et al., do not teach the classifying DLBCL patients survival after an anthracycline-based chemotherapy and an internal control of cellular mRNA, PGK1.

Alizadeh et al., teach a method of classifying patients having a DLBCL and correlating the gene expression in the classification group of patients after treatment of anthracycline-based chemotherapy (page 509, column 2, fig 5 and page 510, line 15-19). Alizadeh et al., disclose the levels of expressing LMO2, BCL-6, BCL-2 from the samples of DLBCL patients (page 508-509 and fig 4).

Goldberg et al., teach expression of mRNA, PGK1, as internal control of a housekeeping gene (para 46).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to make a kit for measuring the expression of genes in the tumor samples from a DLBCL patients of Gordon et al.'s teaching comprising using PGK1 as internal control of Goldberg et al., and the patients with a treatment of anthracycline-based chemotherapy of Alizadeh et al.'s teaching. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to combine the teachings of Gordon et al., Alizadeh et al., and Goldberg et al., to make and use a kit to measure the gene expression of DLBCL tumor samples and classify the DLBCL patients in groups by expression profile measuring by real time RT-PCR on the tumor samples for the patients because Gordon et al., have shown a kit for a cancer diagnosis comprising measuring the expression of a plurality of genes, Alizadeh et al., have show a method of classifying DLBCL patients by expression of plurality of genes comprising LMO2, BCL-6, BCL-2 in patients after treatment of anthracycline-based chemotherapy. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use PGK1 as the housekeeping gene because as shown by Goldberg et al., PGK1 is a known housekeeping gene as an internal control of cellular mRNA.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-4.30pm Monday to Friday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao, Ph.D.
Examiner
Art Unit 1642

LY

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER